Concise Definitive Review

Jonathan E. Sevransky, MD, Series Editor

Septic Cardiomyopathy

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Objectives: To describe, with an emphasis on clinical applications, what is known about the pathophysiology, management, and implications of septic cardiomyopathy in the adult ICU.

Data Sources and Study Selection: A PubMed literature review was performed for relevant articles. Only articles in English that studied human adults with sepsis were included.

Data Extraction and Data Synthesis: Multiple competing definitions for septic cardiomyopathy hinder understanding of this entity. Although many patients with sepsis develop cardiac dysfunction, the impact of septic cardiomyopathy on prognosis and therapy remains to be demonstrated. Treatment of septic cardiomyopathy is aimed at treating the underlying sepsis and providing specific supportive care for cardiogenic shock when present.

Conclusions: Septic cardiomyopathy is an important contributor to organ dysfunction in sepsis. Guided treatment of septic cardiomyopathy may affect patients' prognosis, especially when their cardiac index is substantially decreased. The implication of septic cardiomyopathy for both short- and long-term outcomes is an important area for future investigation. (*Crit Care Med* 2018; 46:625–634)

Key Words: cardiac dysfunction; sepsis; septic cardiomyopathy

Sepsis is a systemic condition of profoundly impaired health in which an infection leads to a dysregulated host response. This inappropriate host response consecutively causes organ dysfunction, disability, and even death (1). By current consensus, sepsis is defined as infection plus organ dysfunction. Septic shock represents the more severe form, in which vasopressor infusions are required to maintain adequate blood pressure, and tissue dysoxia is present, as indicated by lactic acidemia (2). Mortality in patients with sepsis is estimated at 10%, whereas in patients with septic shock, mortality generally exceeds 40% (2).

Central to sepsis, the fate of individual organs is interdependent: failure of one organ often leads to dysfunction or failure of other organs (3). This interdependence is especially evident during cardiovascular failure which diminishes overall blood circulation, thus exacerbating tissue dysoxia, mitochondrial dysfunction, and metabolic dysfunction of tissues. Not surprisingly, progressive cardiovascular collapse is often the penultimate step before death from septic shock (4).

Given the central role of circulatory impairment in disrupting the function of multiple organs, understanding cardiac dysfunction in sepsis is critical. Although others have reviewed septic cardiomyopathy (SCM) in the last 15 years (5–8) (see also references in **online data supplement** [Supplemental Digital Content 1, http://links.lww.com/CCM/D68]), they have generally focused on the causative role of the septic inflammatory milieu in cardiac myocyte dysfunction. In this Concise Definitive Review, we discuss definitions of SCM, briefly review the pathophysiology, and summarize what is known about treatment and management, from a clinical perspective. Our review was guided by the search strategy described in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D68).

DEFINITION AND DIAGNOSIS

A major impediment to understanding SCM is the varied ways it has been defined. Cardiac dysfunction in sepsis can manifest in multiple different ways, including left and/or right

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ventricular impairment during systole or diastole, inadequate cardiac output and oxygen delivery, or primary myocardial cellular injury. In **Table 1**, we present the range of conceptual definitions of SCM and relevant diagnostic testing for each.

When SCM was initially described in the 1980s, it was defined as an acutely depressed left ventricular ejection fraction (LVEF) with ventricular dilation that occurred during sepsis (51–53). These early data suggested that survivors had increased mean end-systolic and end-diastolic volumes as compared to nonsurvivors who had normal ventricular volumes. In retrospect, these differences likely reflected differences in filling pressures and cardiac afterload more than intrinsic myocardial function, a problem compounded by recent changes in fluid resuscitation strategies in sepsis management over ensuing decades. Although several subsequent studies continued to rely on an LVEF-based definition for SCM (9, 10, 15, 54), LVEF has been increasingly acknowledged to be an inaccurate marker of intrinsic cardiac function (16, 17) largely because it depends profoundly on loading conditions (18, 55).

Left ventricular pressure-volume conductance catheters provide another method for measuring real-time cardiac function, allowing more "gold-standard" quantification of systolic and diastolic function independent of loading conditions (56, 57). Although these catheters are highly useful, especially in preclinical models of sepsis, they have not been used in septic patients, thus limiting their applicability in the diagnosis of septic cardiomyopathy (58).

Other echocardiographic variables beyond LVEF have been developed to evaluate cardiac dysfunction in sepsis (Table 1; and online data supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/D68). The myocardial performance index (MPI; also called "the Tei index" [59]) is based on the proportion of the working cycle of the heart that is spent in isovolumic activity during which the heart does not actively circulate blood. (A lower MPI value is associated with better function.) In one prospective cohort of septic patients ($n = 47$), improvement in MPI over 24 hours after admission with severe sepsis or septic shock was associated with a lower 90-day mortality (17% vs 47%) (30).

Another variable, the afterload-adjusted cardiac performance (ACP) is a ratio of measured to predicted cardiac output, adjusted for systemic vascular resistance. These measures are obtained from an indicator-dilution or pulse contour analytic cardiac output monitoring device (see **Appendix** 2 for further details, Supplemental Digital Content 1, http://links.lww.com/CCM/D68). In two studies of septic patients (total $n = 180$), abnormal ACP predicted 30-day mortality (32, 60).

More recently, longitudinal strain, a measure of the deformation of the myocardium, has been introduced as a replacement for LVEF to determine left ventricular (LV) function (61). Myocardial strain can now be measured routinely using speckle-tracking echocardiography, an evaluation of the actual displacement of points in the ventricular wall in relation to each other during systole. By measuring contractility in the actual muscle, strain is less dependent on loading conditions than LVEF (17). In general, longitudinal strain has been shown to detect early changes of myocardial ischemia and correlates extremely well with gold-standard MRI measurements. Importantly, LV longitudinal strain has been demonstrated to be a more sensitive variable than LVEF at diagnosing LV dysfunction in sepsis (17, 18, 21, 62, 63).

Right ventricular (RV) dysfunction also occurs in sepsis, usually in concert with LV dysfunction (64, 65). RV dysfunction can be characterized by dilation or decreased ejection fraction of the RV (66) and may rapidly develop due to increased pulmonary vascular resistance in the setting of acute respiratory distress syndrome (67).

Diastolic dysfunction has also long been noted in many patients with sepsis (68, 69) and often meets the guideline criteria for LV diastolic dysfunction issued by the American Society of Echocardiography (24,26,70) or alternative definitions (e′-velocity < 8 cm/s) (25) or E/e′ ratios at various thresholds (29). To date, RV diastolic dysfunction in sepsis has not been well described. Biomarkers of cardiomyocyte injury are commonly elevated in sepsis (38, 71) and may represent a diagnostic avenue for SCM. However, in sepsis, B-type natriuretic peptide (BNP) and troponin elevations appear to reflect general critical illness and are not specific for SCM (40, 72). Furthermore, the exact etiology of troponin elevations in sepsis is not clear: release of myocardial enzymes may occur independently of cardiomyocyte death or, alternatively, through cell necrosis that is too infrequent to be detected in biopsies.

For the purposes of this discussion, we define SCM broadly as an acute syndrome of cardiac dysfunction that is unrelated to cardiac ischemia in patients with sepsis. While longitudinal strain is a promising measure, we acknowledge that there is not yet sufficient data to inform a single diagnostic measure for SCM.

PATHOPHYSIOLOGY

Among the many factors that play a causal role in septic cardiomyopathy, the sepsis-induced dysregulated inflammatory response has been directly linked to cardiomyocyte dysfunction. Original observations from animal experiments led to an extensive search for specific "myocardial depressant factor(s)." (73) These studies identified cytokines (including interleukin [IL]–1b, tumor necrosis factor-a, IL-6, and the p38 mitogen-activated protein kinases pathway) (74, 75), the complement system, nitric oxide dysregulation (76), high-mobility group box -1 (a damage and signaling molecule implicated in the pathogenesis of sepsis) (77), and lipopolysaccharide as potential causative agents. Recent work has further demonstrated a temporal association between increased cardiomyocyte oxidative stress and the development of septic cardiomyopathy. In support of these findings, the use of reactive oxygen species scavengers in murine models leads to partial reversal of septic cardiomyopathy (78). On the cellular level, these changes were accompanied by increased proteolysis, mitochondrial damage, dysregulated nitric oxide, β-adrenoceptor down-regulation, and calcium mishandling and have thus all been implicated in triggering myocardial dysfunction during sepsis (79–82).

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TABLE 1. Definitions of Septic Cardiomyopathy

Echocardiographic-Based Definitions		Specific Measure	Therapeutic Implications	Benefits and Problems
LV	LV systolic impairment	LVEF (9–13) < 40–50%.	Some experts recommend epinephrine over norepinephrine if LVEF < 45%; levosimendan may improve intermediate outcomes vs dobutamine if LVEF < 45% (14).	LVEF depends on loading conditions and may be diagnostically misleading (15–18).
		Fractional area change (19, 20).	Perhaps similar to LVEF	Deprecated technique likely inferior to LVEF.
		Left ventricular global longitudinal strain (17, 21–23).	None as yet.	Not yet available in real time. Appears superior to LVEF in identifying cardiac dysfunction in sepsis (17, 21).
	LV diastolic dysfunction	e′ velocity (11, 24, 25) and E:e′ ratio (26, 27).	Patients with impaired relaxation may need more fluid (26); patients with pseudonormal diastolic function may be fluid overloaded (28).	Diastolic function depends on fluid status; traditional definitions of diastolic dysfunction unreliable in sepsis (29).
	LV integrated measures	Myocardial performance index (30, 31).	None as yet.	
		Afterload-related cardiac performance (32).	None as yet.	Takes into consideration loading conditions.
		Ventricular arterial decoupling (33, 34).	May ultimately guide choice of vasopressors vs volume expansion	
RV	RV systolic dysfunction	Lateral tricuspid annulus peak systolic velocity (24).	Can identify injurious ventilation (35).	Easily measured in most patients.
		RV peak systolic pressure end-systolic volume relations (35).	None as yet.	
		Tricuspid annular plane systolic excursion.	May identify patients in need of RV support (e.g., vasodilators) (36)	Easily measured in most patients.
	RV diastolic dysfunction	Not well characterized in sepsis.	None as yet.	Has been used as a surrogate for central venous pressure (37).
Nonechocardiographic-Based Definitions		**Specific Measure**	**Therapeutic Implications**	**Benefits and Problems**
Biochemical markers	Cardiomyocyte injury	Troponin (13, 38, 39).	None as yet.	May be a marker of renal failure and/or preexisting obstructive coronary artery disease as well as sepsis.
		Pregnancy-associated plasma protein A (9).	None as yet.	How to classify septic cardiomyopathy based on this laboratory finding is unknown.
	Increased wall stress	Brain natriuretic peptide (13, 20, 40–42).	Possibly can guide fluid loading (43); marker of lower cardiac index (44).	May be compounded by respiratory failure or preexisting cardiac dysfunction.
Hemodynamic markers	Inadequate O_2 delivery	Central venous O_2 saturation/venous oxygen saturation and lactate.	Inotropes likely indicated at some threshold, but threshold not known.	"Goal-directed" therapy ineffective in large randomized controlled trials (45–47) and may be toxic when started late (48).
	Persistent tachycardia after adequate volume expansion	Heart rate.	β1 blockade may be therapeutic (49, 50).	Unclear whether this indicates risk for or presence of cardiomyopathy.

LV = left ventricle, LVEF = LV ejection fraction, RV = right ventricle.

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TABLE 2. Selected Septic Cardiomyopathy Studies

References	Population (*n*)	Measure	Results
Bouhemad et al (19)	Septic shock ($n = 45$)	TTE and cardiac troponin measured days 1–4, 7,10	18% with elevated troponin and decreased LVEF, 18% with increased troponin and diastolic dysfunction.
Brown et al (26)	Severe sepsis or septic shock ($n = 78$)	TTE within 6 hr of admission, between hours 18 and 32, and after resolution of shock	36.5% with diastolic dysfunction at admission, 61.8% with diastolic dysfunction at any time point. Grade 1 diastolic dysfunction MV association with 28-d mortality.
Dalla et al (18)	Severe sepsis or septic shock ($n = 48$) vs trauma ICU patients ($n = 24$) vs healthy controls ($n = 16$)	TTE (including strain) obtained within 48 hr of ICU admit	50% of patients with preserved LVEF had abnormal strain (> −15%).
De Geer et al (22)	Septic shock ($n = 50$)	TTE (including strain) obtained day of ICU admit, during ICU, and after ICU stay	7% of patients with preserved LVEF had abnormal strain (> −15%).
Endo et al (10)	Mechanically ventilated with sepsis ($n = 93$)	TTE on day of enrollment	25% with LVEF < 50%. Not associated with mortality.
Etchecopar-Chevreuil et al (11)	Mechanically ventilated patients with septic shock ($n = 35$)	TEE within 12 hr of admission, following IV fluid and upon resolution of shock	46% with LVEF ≤ 50% at admission; LV diastolic dysfunction 20% at admission.
Landesberg et al (25)	Severe sepsis or septic shock ($n = 262$)	TTE obtained on day of ICU admit and following day	23% had LVEF ≤ 50%; 50% had diastolic dysfunction. Reduced e′-wave and low LV stroke volume index with MV association with mortality.
Lanspa et al (17)	Severe sepsis or septic shock ($n = 89$)	TTE (including strain) obtained within 6 hr of ICU admit, central venous O_2 saturation, serum lactate	60% with abnormal strain.
Mehta et al (85)	Septic shock ($n = 37$)	TTE and cardiac troponin	Elevated troponin correlated with low LVEF. MV association of troponin with mortality.
Ng et al (62)	Septic shock ($n = 33$) and matched controls with sepsis ($n = 29$)	TTE within 24 hr and on recovery, including strain	Strain was more abnormal in septic shock patients. No difference in LVEF.
Nizamuddin et al (30)	Severe sepsis or septic shock ($n = 47$)	TTE at enrollment and 24 hr later to measure MPI	Worsened MPI over 24 hr associated with increased 90-d mortality in MV analysis.
Orde et al (23)	Severe sepsis ($n = 60$)	TTE (including strain) within 24 hr of meeting sepsis criteria	33% with LVEF < 55%, 69% with LV dysfunction using strain. 72% with RV dysfunction using strain. RV free wall longitudinal strain associated with 6-mo mortality.
Palmieri et al (63)	Sepsis or septic shock ($n = 115$)	TTE at admission, including strain	Strain correlated with 7-d mortality. LVEF not associated with mortality.
Pulido et al (24)	Severe sepsis or septic shock ($n = 106$)	TTE within 24 hr of admission	37% with LVEF, 37% LV diastolic dysfunction, 31% with RV dysfunction. No association with mortality.
Rolando et al (27)	Sepsis ($n = 53$)	TTE within 48 hr of admission and on days 7–10	26% with LVEF < 50%. 83% had diastolic dysfunction. 23% had both. E/e′ best predictor of mortality.

(*Comtinued*)

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TABLE 2. (*Continued*). Selected Septic Cardiomyopathy Studies

References	Population (*n*)	Measure	Results
Sato et al[a] (54)	Sepsis or septic shock (*n* = 210)	TTE at admission	14% with LVEF < 50%. LVEF not associated with in-hospital or 30-d mortality.
Shahul et al (21)	Sepsis (*n* = 15) and septic shock (*n* = 35)	TTE (including strain) on enrollment and 24 hr later	Strain worsened significantly in patients with septic shock
Vieillard-Baron et al (12)	Mechanically ventilated patients with septic shock (*n* = 67)	TEE, daily for the first 3 d	60% with LVEF < 45%. LVEF not associated with mortality.
Werdan et al (32)	Sepsis and multiple organ dysfunction syndrome (*n* = 39)	Pulmonary artery catheter measurements of ACP, cardiac troponin measurements	ACP correlated with troponin elevation and mortality.
Wilhelm et al (60)	Sepsis (*n* =141), data collected in emergency department, 24 and 72 hr	Pulmonary artery catheter or pulse contour cardiac output technology measurements of ACP	Nonsurvivors had significantly lower values of ACP.

ACP = afterload-adjusted cardiac performance, LV = left ventricular, LVEF = LV ejection fraction, MPI = myocardial performance index, MV = multivariate analysis, RV = right ventricular, TEE = transesophageal echocardiogram, TTE = transthoracic echocardiogram.

[a]Retrospective studies.

The majority are prospective observational trials.

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On histologic examination, SCM appears as an interstitial inflammatory infiltrate, with increased collagen deposition, intramyocyte lipid accumulation, and contractile apparatus disruption (83, 84). However, biopsies of myocardial tissue from septic patients are rarely available in the acute setting, and peripheral blood may not accurately reflect the inflammatory milieu in the myocardium. Considerable uncertainty therefore exists about how to define SCM noninvasively.

PREVALENCE OF SCM

Septic cardiomyopathy is common, though prevalence varies depending on the definition used (**Table 2**). Risk factors for SCM may include male sex (54), younger age, higher lactate levels at admission, and a history of heart failure, although the last likely reflects preexisting disease (54).

PROGNOSTIC IMPLICATIONS OF SCM

The prognosis associated with SCM is not clear, likely because of the diagnostic variability employed. Studies evaluating outcomes in relation to SCM are found in Table 2. In a systematic review of studies analyzing LVEF and 30-day mortality in patients with severe sepsis or septic shock, LVEF was not a sensitive or specific predictor of mortality (16). In a study of patients with sepsis or septic shock (*n* = 29), when SCM was defined as ejection fraction (EF) less than 50% and a greater than 10% decrease compared with baseline, there was no significant difference in either the in-hospital or 30-day mortality between patients with and without SCM (54). It is possible that the lack of association with mortality is due to the dependence of LVEF on loading conditions: profound vasoplegia associated with severe shock may elevate LVEF while LVEF may be depressed by effective vasopressor infusions. Similarly, profoundly decreased preload may increase LVEF measurements, whereas adequate volume expansion may decrease LVEF. A decrease in RV ejection fraction has also been associated with worse prognosis (66, 86, 87).

Other echocardiographic variables may also be suitable for prognostication. In a study of patients with sepsis or septic shock (*n* = 115), LVEF and LV longitudinal strain were measured at admission. In these patients, overall 28-day mortality was 30%. Strain correlated significantly with mortality, whereas EF did not (63). Similarly, recent work revealed that in patients with severe sepsis worsening strain predicts short-term mortality independent of Sequential Organ Failure Assessment scores. However, in another small study (*n* = 60), no association between mortality and strain was identified.

Diastolic function has also been evaluated as a prognostic indicator in sepsis, and a larger study of 262 patients found septic diastolic dysfunction to be a predictor of mortality (25). Grade of diastolic dysfunction was not obtained in this study. A smaller study (*n* = 78) suggested that grade I diastolic dysfunction was associated with increased mortality in sepsis and septic shock patients, whereas grades II and III diastolic dysfunction was not (26).

Among serum biomarkers, elevated troponin levels appear to be associated with increased mortality in sepsis (88), but this effect largely disappears when correcting for severity of illness (89, 90). Similarly, BNP's association with mortality is not significant when the level of illness is taken into account (40–42, 90, 91). Although procalcitonin is mainly used as an indicator of bacterial infection, this biomarker may also reflect an increased mortality in patients with cardiovascular disease (92, 93). Studies specific to diagnosis and prognosis of SCM using such biomarkers will be needed to better define their utility.

An important unanswered question is when to consider unstable coronary artery disease (or even, rarely, septic embolism into the coronary circulation) as a differential diagnosis

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of apparent SCM. Electrocardiographic ST segment elevations (94, 95), regional wall motion abnormalities, and elevated troponin (71) appear to lack specificity for distinguishing the phenomena diagnostically. The criteria for selecting patients who might benefit from specific cardiac therapy thus remain an area of important future research. As the current evidence is insufficient to delineate strict guidelines for clinical management of acute coronary syndrome (ACS) in patients with sepsis and septic shock, we follow current recommendations for diagnosis and treatment of ACS, while tailoring testing and therapy (including anticoagulation) for patients based on their other risk factors, laboratory biomarkers, and hemodynamics.

Although patients with sepsis have an elevated risk for cardiovascular disease that is similar to the risk for other acutely ill patients (96, 97), very little is known about long-term cardiovascular outcomes of patients who suffered from SCM. Most studies have suggested that recovery from SCM is prompt but rarely provide the data to support this supposition. In one study of septic shock patients, 46% had LV dysfunction and 34% of patients died in the hospital (11). Surviving patients were followed 2 weeks for recovery, and EF recovered in all patients (Philippe Vignon, private communication, May 4, 2017). Further studies are needed to assess the progression of SCM over time in light of the newer diagnostic strategies mentioned above.

THERAPEUTIC IMPLICATIONS OF SCM

There are no evidence-based recommendations for the management of SCM. The most commonly applied approach is to treat the underlying disease, that is, sepsis, according to best practices (98), as treatment directed at inflammatory markers in sepsis has been ineffective in humans. However, as understanding of the pathophysiology of SCM continuously progresses, novel ways to reduce the associated morbidity and mortality are bound to be developed.

Given the possibility of relative myocardial suppression and the high oxygen consumption in sepsis, investigators have sought to determine whether artificially increasing cardiac output may be beneficial. Notably, studies that evaluated increasing cardiac output to "supranormal" levels (cardiac index > 4.5 L/min/m^2) have not improved outcomes (48, 55). Similarly, a reported benefit of "goal-directed" therapy to patients with sepsis during the first 6 hours of the emergency department stay (99) has not been reproduced in multicenter trials (45–47). As a consequence, dobutamine is no longer recommended routinely for sepsis based solely on measurement of central venous oxygen saturation (Scv_{O_2}) less than 70% (2). Similarly, levosimendan, a calcium sensitizer that functions not only as an inotrope but also as a lusitrope, was reported in a small series with possible benefit in increasing cardiac index (14, 100). However, in a multicenter randomized trial (n = 516), levosimendan did not result in a lower mortality rate or less severe organ dysfunction among patients with septic shock (101).

Taking an opposite approach, a pilot trial of esmolol to optimize cardiac loading conditions in tachycardiac patients with septic shock suggested mortality benefit (102) but its results have not been reproduced, and the trial faced concerns about extensive concomitant use of levosimendan (subsequently found to lack efficacy in sepsis as noted above [101]) and extremely high hospital mortality in the study population (103).

SEPSIS-INDUCED CARDIOGENIC SHOCK

While SCM is common, the prevalence and implications of frank cardiogenic shock complicating sepsis are poorly understood. Limited studies that were conducted decades ago have documented the occurrence of a sepsis-induced cardiogenic shock syndrome. In 1990, Jardin et al (105) described six patients with depressed LVEF, only one of whom developed circulatory collapse. The mean cardiac index in this group was 2.2 L/min/m^2 and mean LVEF was 21%. In 1978, Weil et al (106) described eight patients who died of bacteremia with a cardiac index under 3 L/min/m^2 but many of them may have been under-resuscitated as judging by circulating blood volume. Few, if any, recent studies have explicitly described the outcomes among patients with frankly depressed cardiac index (i.e., < 2.1 L/min/m^2) in septic shock.

For mild to moderate sepsis-induced cardiogenic shock, inotrope infusions have long been an accepted standard of therapy, albeit without randomized controlled trials to guide use or indicate thresholds for intervention. Annane et al (104) showed no difference between epinephrine alone versus norepinephrine plus dobutamine in an unselected cohort of septic patients (n = 330). We suspect, on the basis of clinical experience but limited scientific evidence, that the combination of a low Scv_{O_2} (e.g., < 50–60%) in the setting of an elevated lactate (e.g., > 4 mmol/L) would motivate most experienced clinicians to initiate inotrope infusions in an adequately volume-expanded patient. (Of note, we consider a patient to be adequately volume expanded if there is no further increase in cardiac output with increased preload [107].)

Based on experience with primary cardiogenic shock and the pediatric practice of mechanical support for refractory septic shock (108, 109), some centers have employed veno-arterial extracorporeal membrane oxygenation (VA ECMO) to treat patients with sepsis-induced, inotrope-refractory cardiogenic shock. Bréchot et al (110) described a case series of 14 adults in France with 71% survival after VA ECMO for sepsis-induced cardiogenic shock. Huang et al (111) described 52 patients in Taiwan with much lower (15%) survival after receiving extracorporeal membrane oxygenation for refractory septic shock (notably not for sepsis-induced cardiogenic shock), a finding that was accentuated in patients over age 60 years, none of whom survived. Average survival with VA ECMO for other indications is approximately 40% (112). These and similar experiences are only detailed in case reports (113–119); trials of mechanical support for sepsis-induced cardiogenic shock have not been performed to date nor have clear criteria been proposed that aid to determine which patients with sepsis-induced cardiogenic shock might be the ideal candidates for this treatment.

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RESEARCH PRIORITIES

A central shortcoming in reviewing the current knowledge on SCM is the lack of a unifying definition and diagnostic criteria for the syndrome. Studies of SCM have employed different inclusion and exclusion criteria, making it difficult to delineate SCM as a clinical entity. Thus, important work remains to be done in validating consistent definitions of SCM, especially as it pertains to differences in treatment and/or outcomes. To estimate the patient-specific risk for developing septic cardiomyopathy, novel diagnostic avenues are required. These could include personalized genome (or RNA) sequencing and phenotyping of individualized cardiomyocytes obtained from patient-derived induced pluripotent stem cells (120). We are skeptical that targeting individual inflammatory cytokine pathways in septic cardiomyopathy will lead to significant diagnostic or therapeutic advances, as most of these interventions in sepsis have proved ineffective (121).

Additional epidemiologic work will be important to establish risk factors for development of septic cardiomyopathy for those with underlying baseline cardiovascular disease. Although we presume that patients with baseline cardiovascular dysfunction will have worse cardiac function during sepsis, this is difficult to establish given the difficulties in determining baseline echocardiographic variables among patients presenting with sepsis.

Specific aspects of SCM merit further investigation. As the correct balance of cardiac output and adrenergic tone is critical for hemodynamic stability in septic patients, several recent small studies have advocated the use of beta-blocker therapy for patients with septic shock (49,50,122). Given the dynamic nature of the baroreflex tone during sepsis, explicit protocols for titration of beta-blocker infusions will be critical for evaluating the utility of beta blockade in sepsis. Whether a dominantly neurohormonal or hemodynamic model of beta blockade in septic shock will be optimal to guide adrenergic therapy in SCM remains to be explored. Studies of advanced cardiac failure from other causes suggest the relevance of neurohormonal rather than purely hemodynamic regulation (123–125).

Long-term outcomes are of increasing priority for studies of critical illness (126–129). Patients after sepsis are at sustained risk for late morbidity and mortality (130–132), which appears at least partially due to an increased incidence of cardiovascular events (97, 133). Whether these are related to SCM is not known. Postacute follow-up for SCM is therefore an important research and clinical priority.

CONCLUSIONS

Cardiac dysfunction during sepsis is an important clinical and research problem, diagnostically, therapeutically, and for prognostication. Septic cardiomyopathy is common and may occasionally be associated with frank cardiogenic shock, requiring inotropic support and possibly mechanical support. As prior research in the field has been limited by poorly differentiating diagnostic strategies (most importantly, the reliance on LVEF), substantial new research is needed to improve understanding of SCM. Such studies would help to optimally define and classify SCM, identify its long-term effect on the patient's health, and promote new treatment options and management strategies.

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